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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,350	07/11/2003	John K. Cini	MXI-285	6687

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,350	CINI ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/18/2007 & 04/23/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,9-13,15,17-21,23,25-27,29-31,33 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,9-13,15,17-21,23,25-27,29-31,33 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/19/2006, 01/18/2007, 05/16/2007, 12/05/2007.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/18/2007 and 04/23/2007 are entered. Claims 1, 3-5, 9-13, 15, 17-21, 23, 25-27, 29-31, 33, and 35-39 are pending and under consideration.

Withdrawn Objections and/or Rejections

The rejection of claims 1, 4, 9, 10, 12, 13, 15, 17-21, 23, 26, 29-31, 33, and 35-39 under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 5,217,954 A, 8 June 1993) in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000) is withdrawn in view of amended claims.

The rejection of claims 1, 3, 4, 6, 9-15, 21, 23, 25, 26, 28-33, and 39 under 35 U.S.C. 103(a) as being unpatentable over Kerwin et al. (US Patent No. 5,929,031, 27 July 1999) in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000) is withdrawn in view of amended claims.

Information Disclosure Statement

The information disclosure statement filed on 10/19/2006, 01/18/2007, 05/16/2007, and 12/05/2007 have been considered by the examiner.

Claim Rejection —35 USC § 112, 1st paragraph

(i). The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

(ii). Claims 1, 3-5, 9-13, 15, 17-21, 23, 25-27, 29-31, 33, and 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an antibody formulated with DTPA and DEF, does not reasonably provide enablement for a composition comprising a fragment of an antibody formulated with DTPA and DEF or a pharmaceutical composition comprising an antibody or a fragment thereof formulated with DTPA and a high concentration of DEF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in

the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 1, 3-5, 9-13, 15, 17-21, 23, 25-27, 29-31, 33, and 35-39 are drawn to a composition comprising an antibody or a fragment thereof formulated with DTPA and DEF or a method of preparing such a composition. The claims are broad because the claims do not limit the fragment of antibody to be an antigen-binding fragment and because the claims recite a fragment of an antibody that encompass, for example, a single amino acid residue of an antibody. The specification fails to provide guidance on how to make and use a composition comprising a fragment of antibody formulated with DTPA and DEF. Moreover, claims 21 and 39 are drawn to a pharmaceutical composition comprising an antibody or a fragment thereof formulated with DTPA and DEF. The prior art teaches that the acute and chronic toxicity of deferoxamine is relatively high, potentially causing hypotension when administered intravenously (US Patent No. 5,268,165, bottom of column 3). Thus, a composition comprising a high concentration of deferoxamine would not be used by one of skilled in the art for pharmaceutical purposes. Accordingly, The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. It is suggested that "fragment thereof" be amended to "an antigen-binding fragment thereof".

Claim Rejections under 35 USC § 103 (a)

(i). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(ii). Claims 1, 3-5, 9, 10, 12, 13, 15, 17-21, 23, 25-27, 29-31, 33, and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al. (US 5,217,954 A, 8 June 1993) in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000), Packer et al. (*Methods in Enzymology*, Volume 186: 41-42, 1990), and Akers (*J. Par. Sci. Tech.* 36:222-228, 1982).

Foster et al. teach protection of bFGF from oxidation during storage and clinical use. Foster et al. teach the presence of certain chelating agents effectively stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation (bottom of column 1). Specifically, Foster et al. teach preparation of a pharmaceutical formulation comprising a protein, bFGF, a stabilizing chelator, such as DTPA or EGTA. The formulation comprises optionally an agent for tonicity, a preservative or other auxiliaries, such as mannitol, glycerol, sodium chloride (see, e.g., columns 3-6) or Tris (Example 1). The concentration of chelating agent is present in amounts of from about 0.001% to about 2.0% percent (weight/weight) of the overall formulation (the 4th paragraph of column 4), which is within the recited concentration of DTPA, about 1 μM to about 10 mM in claim 4, and recited DEF concentration, about 1 μM to about 5 mM.

Foster et al. teach that the chelators are used individually or in combinations (bottom of column 1 to top of column 2) and that a stabilizer can be used in combination with other stabilizers, such as citrate (the 2nd paragraph of column 5) and that the formulation can be prepared in a buffer system, such as sodium citrate (the 4th paragraph of column 5), with the pH of the formulation being from about 2 to about 8 (the 6th paragraph of column 5). Foster et al. teach continuous release formulations, including microcapsules that are essentially small particles of active compounds embedded in a suitable polymer (the 4th paragraph of column 5). Foster et al. further teach that the formulation comprises 0.01%-10% FGF in solution (lines 48-49 of column 6, and in Example 4, the concentration of FGF is 100 ug/ml).

Foster et al. do not teach a composition comprising an antibody, a monoclonal antibody or a human antibody formulated with DTPA and DEF or a method preparing such a composition.

Hagiwara et al. teach preparing a stable human monoclonal antibody preparation (see, e.g., Abstract). Hagiwara et al. also teach human monoclonal antibodies have an undesirable property that they easily aggregate and precipitate in a solution state (the 4th paragraph of column 1).

Packer et al. teach a chelating agent, desferrioxamine (deferoxamine or DEF), which suppress iron-dependent generation of ·OH from H_2O_2 (2nd paragraph of page 42).

Therefore, it would have been obvious to one of skilled in the art to modify the method of Foster et al. to prepare a composition comprising a human monoclonal antibody, formulated with DTPA and DEF with a reasonable expectation of success. One would have been motivated to do so because Foster et al. teach that the chelators can be used either individually or in combination (bottom of column 1 to top of column 2) and Akers teaches that the use of combination of antioxidant in the same formulation produces a synergistic effect (page 227, the 2nd paragraph). Moreover, a human monoclonal antibody is, in essence, a protein and shares the basic components—amino acids with a protein, including cysteine residues, which are susceptible to oxidation. A human monoclonal antibody possesses characteristics that tend to form aggregates as taught by Hagiwara et al. (the 4th paragraph of column 1). The use of DTPA and DEF would stabilize a composition comprising a human monoclonal antibody.

(iii). Claims 1, 3-5, 9-13, 15, 17, 18, 21, 23, 25-27, 29-31, 33, 35, 36, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerwin et al. (US Patent No. 5,929,031, 27 July 1999), and further in view of Hagiwara et al. (U.S. Patent No. 6,165,467, December 26, 2000), Packer et al. (*Methods in Enzymology*, Volume 186: 41-42, 1990), and Akers (*J. Par. Sci. Tech.* 36:222-228, 1982).

Kerwin et al. teach preparation of a pharmaceutical composition (column 8), which comprises a protein, hemoglobin at a concentration of 0.001% to 90% (w/v) (4 mg/ml and 100 mg/ml were used in Example 1 and 2), a reducing agent, such as sodium

ascorbate or 0.03% (w/v) polysorbate 80 (lines 24-25 of column 13), 0-200 μM of one or more chelators, such as DTPA, EGTA (lines 45-51 of column 8). The formulation may also comprise one or more buffers, such as citrate or Tris (line 65 of column 12), and salts, such as sodium chloride (lines 32-35). The pH of the composition can be at about 6.5-9.5 (line 52 of column 8).

Kerwin et al. do not teach a composition comprising an antibody, a monoclonal antibody or a human antibody formulated with DTPA and DEF or a method preparing such a composition.

Hagiwara et al. teach preparing a stable human monoclonal antibody preparation (see, e.g., Abstract). Hagiwara et al. also teach human monoclonal antibodies have an undesirable property that they easily aggregate and precipitate in a solution state (the 4th paragraph of column 1).

Packer et al. teach a chelating agent, desferrioxamine (deferoxamine or DEF), which suppress iron-dependent generation of ·OH from H_2O_2 (2nd paragraph of page 42).

Therefore, it would have been obvious to one of skilled in the art to modify the method of Kerwin et al. to prepare a composition comprising a human monoclonal antibody formulated with DTPA and DEF with a reasonable expectation of success. One would have been motivated to do so because Kerwin et al. teach that one or more of chelators

can be used in a formulation (lines 45-51 of column 8) and Akers teaches that the use of combination of antioxidant in the same formulation produces a synergistic effect (page 227, the 2nd paragraph). Moreover, a human monoclonal antibody is, in essence, a protein and shares the basic components—amino acids with a protein, including cysteine residues, which are susceptible to oxidation. A human monoclonal antibody possesses characteristics that tend to form aggregates as taught by Hagiwara et al. (the 4th paragraph of column 1). The use of DTPA and DEF would stabilize a composition comprising a human monoclonal antibody.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Primary Examiner
January 8, 2008

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PRIMARY EXAMINER